Stochastic Molecular Optimization Using Generalized Simulated Annealing

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ABSTRACT: We propose a stochastic optimization technique based on a generalized simulated annealing (GSA) method for mapping minima points of molecular conformational energy surfaces. The energy maps are obtained by coupling a classical molecular force field (THOR package) with a GSA procedure. Unlike the usual molecular dynamics (MD) method, the method proposed in this study is force independent; that is, we obtain the optimized conformation without calculating the force, and only potential energy is involved. Therefore, we do not need to know the conformational energy gradient to arrive at equilibrium conformations. Its utility in molecular mechanics is illustrated by applying it to examples of simple molecules (H_2O and H_2O_3) and to polypeptides. The results obtained for H_2O and H_2O_3 using Tsallis thermostatistics suggest that the GSA approach is faster than the other two conventional methods (Boltzmann and Cauchy machines). The results for polypeptides show that pentalanine does not form a stable α-helix structure, probably because the number of hydrogen bonds is insufficient to maintain the helical array. On the contrary, the icoalanine molecule forms an α-helix structure. We obtain this structure simulating all Φ, Ψ pairs using only a few steps, as compared with conventional methods. © 1998 John Wiley & Sons, Inc.
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Introduction

Molecular systems can exist in different conformational geometries, corresponding to different three-dimensional arrangements of atoms in a structure. The number of conformations allowed increases with molecular size. In particular, macromolecules of biological interest present a large number of local minima (or local equilibrium conformations). Indeed, geometry optimization is a crucial first step in any molecular modeling strategy. The main obstacle in this field is to find a global minimum and to not get trapped in one of the many local minima. The usual optimization methods applied to quantum and classical molecular physics are based on the gradient descent approach, which indistinctly selects both global and local minima. Therefore, in locating the global minimum, brute force has been the usual tool.

To overcome these difficulties, we propose a stochastic strategy to determine optimized geometries based on the generalized simulated annealing (GSA) algorithm.[1] In this proposal, the localization of the global minimum of any potential function (cost function) is obtained using the Monte Carlo method in an annealing procedure. This procedure maps various intermediary equilibrium states and goes at the end to the global minimum.

Our procedure consists of using the molecular conformational energy, obtained from a classical parameterized force field (THOR package [2, 3]), with the geometries obtained randomly for the GSA routine. Following the Monte Carlo procedure, we introduce an artificially decreasing temperature, which allows the storage of local minima through an I/O statement. At the end of the optimization process, the system will be inside the basin of the global minimum (or, if there is degeneracy, within one of the global minima).

The simulated annealing procedure is widely used in the minimization of nonconvex (multiple minima) functions, in different subjects, as an alternative to gradient descent methods. Some of the recent studies related to GSA include: the fitting of curves by simulated annealing[4]; one study[5] in which the investigators applied GSA to study the conformational analysis of a particular tetrapeptide; and, more recently, application[6] of GSA in the case of optimization of nonlinear gravity models.

The stochastic molecular optimization (SMO) method is a promising step toward understating the behavior of macromolecules in terms of interactions on the atomic level. This method is appropriate to analyze the most probable macromolecular conformational state. As an added bonus, conformational energy hypersurface mapping results from the search for the global minimum conformation. Furthermore, unlike the usual molecular dynamics (MD) method, the SMO is force independent; that is, we obtain the optimized conformation without calculating the force, and only potential energy is involved. Therefore, we do not need to know the conformational energy gradient to arrive at equilibrium conformations.

In the next section, we present the GSA algorithm used for recovering the global minimum. We then discuss the computational code used by THOR for calculating the potential energy of geometries obtained randomly from the GSA routine. We also present results concerning some molecular structures of simple molecules (H_2O and H_2O_3) and polypeptides.

Generalized Simulated Annealing

Simulated annealing methods have been applied successfully in the description of a variety of global extreme problems. Simulated annealing methods have attracted significant attention due to their suitability for large-scale optimization problems, especially for those in which a desired global minimum is hidden among many local minima. The basic aspect of the simulated annealing method is that it is analogous to thermodynamics, especially in regard to the way that liquids freeze and crystallize, or that metals cool and anneal. The first nontrivial solution along this line was provided by Kirkpatrick et al.[8,9] for classical systems, and further extended by Ceperley et al.[10] to quantum systems. It strictly follows the quasi-equilibrium Boltzmann–Gibbs statistics using a Gaussian visiting distribution, and is sometimes referred to as *classical simulated annealing* (CSA) or the *Boltzmann machine*. The next step of interest in this subject area was Szu's proposal[11] to use a *Cauchy–Lorentz visiting distribution*, instead of a Gaussian distribution. This algorithm is referred to as *fast simulated annealing* (FSA) or the *Cauchy machine*.

On the other hand, a GSA or *Tsallis machine* approach, which closely follows the recent Tsallis

statistics,[12,13] has been proposed by Stariolo and Tsallis[1]; GSA generalizes both the FSA and CSA procedures.

We have implemented the GSA algorithm as a method to calculate the minimum energies of conformational geometries for different molecular structures. This technique can be indistinctly applied in quantum[7] or classical methods. In our case, we used the latter. GSA methods are based on the correlation between the minimization of a cost function (conformational energy) and the geometries randomly obtained through slow cooling. In this technique, an artificial temperature is introduced and gradually cooled in complete analogy with the well-known annealing technique, frequently used in metallurgy when a molten metal reaches its crystalline state (global minimum of the thermodynamics energy). In our case, the temperature is intended as an external noise.

The artificial temperature (or set of temperatures) acts as a convenient stochastic source for eventual detrapping from local minima. Near the end of the process the system is hopefully within the attractive basin of the global minimum. The challenge is to reduce the temperature as quickly as possible and still have the guarantee that no irreversible trapping at any local minimum has occurred. More precisely, we search for the quickest annealing (approaching a quenching) that maintains the probability of finishing within a global minimum of 1.

The procedure to search the minima (global and local) or to map the energy hypersurface consists in comparing the conformational energy for two consecutive random geometries, $\mathbf{x}_{t+1}$ and $\mathbf{x}_t$, obtained from the GSA routine. $\mathbf{x}_t$ is an N-dimensional vector that contains all atomic coordinates (N) to be optimized. The geometries, for two consecutive steps, are related by:

$$\mathbf{x}_{t+1} = \mathbf{x}_t + \Delta\mathbf{x}_t \tag{1}$$

where $\Delta\mathbf{x}_t$ is a random perturbation on the atomic position.

To generate the random vector $\Delta\mathbf{x}_t$, the present GSA routine used an extension of the procedure used in ref. 1. We calculated the $\Delta\mathbf{x} = \mathbf{g}^{-1}(\omega)$ using a numerical integration of the visiting distribution probability, $g_{q_V}(x)$. ω is a random vector $[0, 1]$ obtained from an equiprobability distribution and $\mathbf{g}^{-1}$ is the inverse of the integral of $g_{q_V}(x)$ given by:

$$\mathbf{g}^{-1}(\omega) = \text{inverse}\left(\int_{-\infty}^{x} g_{q_V}(x)\,dx\right) = \text{inverse}(\omega) \tag{2}$$

$$\mathbf{g}^{-1}(\omega) = \text{inverse}\left(\int_{-\infty}^{x}\left(\frac{q_V-1}{\pi}\right)^{1/2}\frac{\Gamma\left(\frac{1-\frac{1}{2}(q_V-1)}{q_V-1}\right)}{\Gamma\left(\frac{1}{q_V-1}-\frac{1}{2}\right)}\frac{\left[T_{q_V}^{V}(t)\right]^{-\frac{1}{3-q_V}}}{\left\{1+(q_V-1)\dfrac{(x)^2}{\left[T_{q_V}^{V}(t)\right]^{\frac{2}{3-q_V}}}\right\}^{\frac{1}{q_V-1}-\frac{1}{2}}}\,dx\right)$$

where q_A (q_V) is the *acceptance index* (*visiting index*).

$$g_{q_V}(\Delta x_t) = \left(\frac{q_V-1}{\pi}\right)^{1/2}\frac{\Gamma\left(\frac{1-\frac{1}{2}(q_V-1)}{q_V-1}\right)}{\Gamma\left(\frac{1}{q_V-1}-\frac{1}{2}\right)}\frac{\left[T_{q_V}^{V}(t)\right]^{-\frac{1}{3-q_V}}}{\left\{1+(q_V-1)\dfrac{(\Delta\mathbf{x}_t)^2}{\left[T_{q_V}^{V}(t)\right]^{\frac{2}{3-q_V}}}\right\}^{\frac{1}{q_V-1}-\frac{1}{2}}} \tag{3}$$

The integral of $g_{q_V}(x)$ has an analytical solution only in case of $(q_A; q_V) = (1;1)$ or $(q_A; q_V) = (1;2)$. For the general case,[14] it is necessary to make a numerical integration. In this study, $\mathbf{g}^{-1}$ has been calculated using a series integration and taken with the inverse of a polynomial series, whose expansion is cut off at order 17.

The integral in eq. (2) can be written as:

$$\omega = \omega(x) = \left(\frac{q_V - 1}{\pi}\right)^{1/2} \frac{\Gamma\left(\dfrac{1 - \frac{1}{2}(q_V - 1)}{q_V - 1}\right)}{\Gamma\left(\dfrac{1}{q_V - 1} - \dfrac{1}{2}\right)} \times \int_{-\infty}^{x} dx \frac{a}{(1 + bx^2)^c} \quad (4)$$

where

$$a = \left[T_{q_V}^V(t)\right]^{-\frac{1}{3-q_V}}, \; b = \frac{(q_V - 1)}{\left[T_{q_V}^V(t)\right]^{\frac{2}{3-q_V}}},$$

and

$$c = \frac{1}{q_V - 1} - \frac{1}{2}.$$

Solving eq. (4) using the power series, we have:

$$\omega = \frac{1}{2} + ax - \frac{1}{3}abcx^3 + \frac{1}{5}\left(\frac{1}{2}ac^2b^2 + \frac{1}{2}acb^2\right)x^5 + \cdots \quad (5)$$

or:

$$\omega(x) = \omega_o + A_1 x + A_2 x^3 + A_5 x^5 + \cdots = \omega_o + \sum_{n=1}^{\infty} A_n (x - x_o)^n \quad (6)$$

We ask for the inverse function $\mathbf{g}^{-1} = x = x(\omega)$, such that $x(\omega) - x = 0$. From eq. (6) we see that the inverse function may be expressed in terms of a power series:

$$x(\omega) = x_o + \sum_{n=1}^{\infty} B_n (\omega - \omega_o)^n \quad (7)$$

by virtue of the theorem: *Let* $\omega(x)$ *be analytic at* $x = x_o$, *and* $[d/dx]\omega(x_o) \neq 0$, *then the inverse of* $\omega(x)$ *exists and is analytic in a sufficiently small region about* $\omega(x_o)$ *and its derivative is* $1/[d/dx]\omega(x_o)$.

The coefficients, B_n, may be expressed in terms of A_n by introducing eq. (7). However, it is possible to derive the coefficients more elegantly by employing Cauchy's formula. In this case, the B_n values take the general form:

$$B_n = \frac{1}{nA_1^n} \sum_{\alpha,\beta,\gamma\cdots} (-1)^{\alpha+\beta+\gamma+\cdots} \times \frac{(n)(n+1)\cdots(n-1+\alpha+\beta+\gamma+\cdots)}{\alpha!\beta!\gamma\cdots} \times \left(\frac{A_2}{A_1}\right)^{\alpha}\left(\frac{A_3}{A_1}\right)^{\beta}\cdots \quad (8)$$

The first few B_n coefficients can be expressed as:

$$B_1 = \frac{1}{A_1}$$

$$B_2 = -\frac{A_2}{A_1^3}$$

$$B_3 = \frac{1}{3A_1^3}\left[\frac{3\cdot 4}{2!}\left(\frac{A_2}{A_1}\right)^2 - \frac{3}{1!}\left(\frac{A_3}{A_1}\right)\right]$$

$$B_4 = \frac{1}{4A_1^4}\left[-\frac{4\cdot 5\cdot 6}{3!}\left(\frac{A_2}{A_1}\right)^3 + \frac{4\cdot 5}{1!1!}\left(\frac{A_2}{A_1}\right)\left(\frac{A_3}{A_1}\right) - \frac{4}{1!}\left(\frac{A_4}{A_1}\right)\right] \quad (9)$$

This last inversion was introduced in the GSA package,[14] whereas the original proposition[1] used a Lévy–Flight distribution as the visiting distribution.

In summary, the whole algorithm for mapping and searching the global minimum of the energy is:

(i). Fix the parameters $(q_A; q_V)$ [recall that $(q_A; q_V) = (1;1)$ and $(1;2)$, respectively, correspond to the Boltzmann and Cauchy machines]. Start, at $t = 1$, with arbitrary internal coordinates and a high enough value for $T_{q_V}(1)$ (*visiting temperature*) and cool as follows:

$$T_{q_V}^V(t) = T_{q_V}(1)\frac{2^{q_V - 1} - 1}{(1 - t)^{q_V - 1} - 1} \quad (10)$$

where t is the discrete time corresponding to computer iteration.

(ii). Then, randomly generate the new atomic coordinate $\mathbf{x}_{t+1}$ from $\mathbf{x}_t$ as given by the visiting distribution probability, g_{q_V}, as follows:

$$\mathbf{x}_{t+1} = \mathbf{x}_t + \mathbf{g}^{-1}(\omega) \tag{11}$$

For sufficiently long time simulations this procedure assures that the system can both escape from any local minimum and can explore the entire energy hypersurface. This equation is used in the GSA routine and differs from the general proposal given in ref. 1, because we built a minimization vector using eq. (1). This change is due to the isotropy of the space used[14] and not due to the simulation of a Lévy–Flight stable stochastic process, such as in ref. 1.

(iii). Then, calculate the conformational energy, $E(\mathbf{x}_{t+1})$, from the new molecular geometry by using the classical force field computational code (THOR). The new energy value will be accepted following the relationship:

if $E(\mathbf{x}_{t+1}) \leq E(\mathbf{x}_t)$, replace $\mathbf{x}_{t+1}$ by $\mathbf{x}_t$;

if $E(\mathbf{x}_{t+1}) > E(\mathbf{x}_t)$, run a random number $r \in [0, 1]$;

if $r > P_{q_A}$ (*acceptance probability*), retain $\mathbf{x}_t$; otherwise, replace $\mathbf{x}_t$ by $\mathbf{x}_{t+1}$.

Or, the algorithm:

$$P_{q_A}(\mathbf{x}_t \rightarrow \mathbf{x}_{t+1}) = \begin{cases} 1 & \text{if } E(\mathbf{x}_{t+1}) \leq E(\mathbf{x}_t) \\ \dfrac{1}{1 + \left[1 + (q_A - 1)(E(\mathbf{x}_{t+1}) - E(\mathbf{x}_t))/T_1^A(t)\right]^{\frac{1}{q_A - 1}}} & \text{if } E(\mathbf{x}_{t+1}) > E(\mathbf{x}_t) \end{cases} \tag{12}$$

with $T_{q_A}^A(t) = T_{q_V}^V(t)$. P_{q_A} is the acceptance probability function.

(iv). Calculate the new temperature, $T_{q_V}^V(t)$, using eq. (10), and go back to (ii) until the $E(\mathbf{x}_t)$ is reached within the desired precision.

To make clear the procedure to construct the computational code used, we present the flow chart in Figure 1.

In the next section, we consider the THOR molecular modeling computational code.

THOR Molecular Force Field

The THOR program was developed to be a comprehensive and flexible tool to investigate macromolecular structures of biological interest like proteins and membranes. The computational code is based on a classical force field. Both molecular dynamics and optimization gradient methods are available. THOR is also now able to attain conformational structures with SMO methods. The choice of either of these methods is based on user need. If we need dynamics properties (a local minimum structure) we can use MD (gradient approach). If it is better to use conformational energy hypersurface mapping, or global minimum localization, we must choose the SMO method.

It is well known that the biological activity depends on the spatial conformation acquired by macromolecules in the physiological medium. The action of hormones and drugs is also dependent on the molecular structure of the target molecules. In recent years, models developed for biological molecules allowed[15] significant advances by proposing new molecular architectures able to satisfy specific properties, increasing their biological efficiency.

Most molecular modeling has been restricted to molecules independent of environmental solvent. However, many important biological functions are related to the nature and to the heterogeneity of the solvent medium. For example, proteins that compose membranes depend, at the molecular level, on the inhomogeneous medium composed

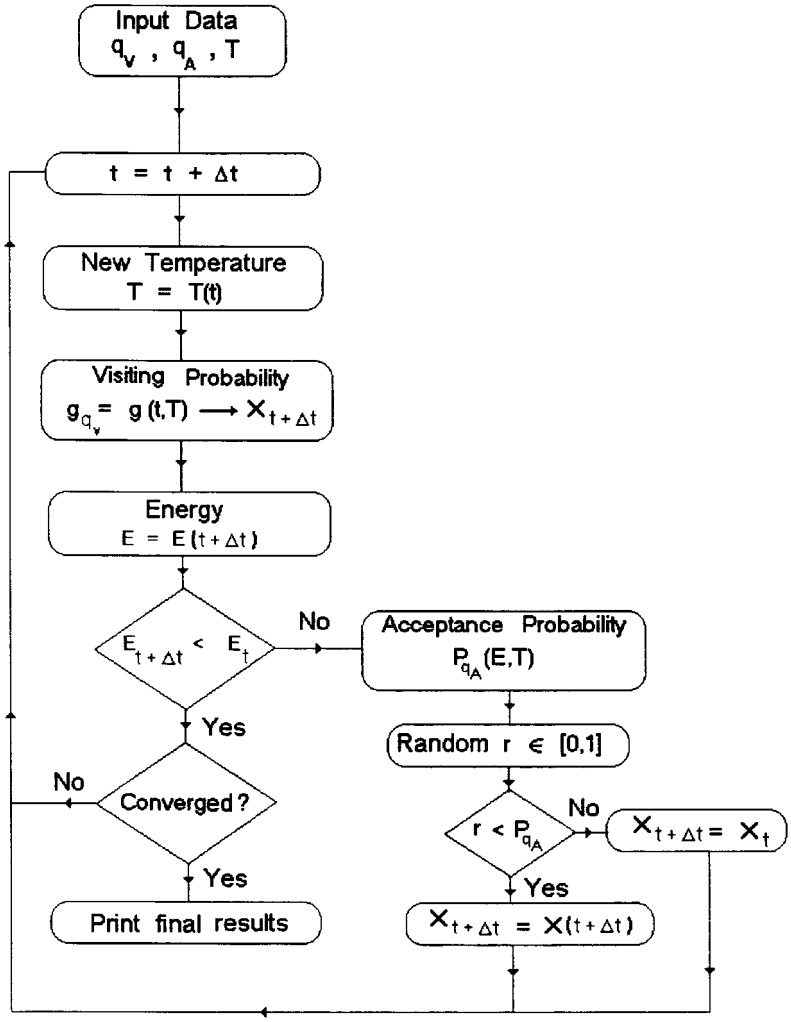

FIGURE 1. Procedure used to make the coupling between the molecular mechanics package (THOR) and generalized simulated annealing (GSA).

by the membrane and its neighborhood. In biological membranes, fundamental molecular properties are associated with the conformational changes brought about by changes in the solvent medium; that is, between the membrane lipidic phase and its adjacent medium water phase. Therefore, THOR is able to simulate this interface and to insert molecules into this heterogeneous medium.[3] Furthermore, THOR is able to accomplish this for isolated molecules as well as for complex sets of molecules; for example, simulating a membrane structure or enzyme–inhibitor complexes.

THOR molecular interaction is simulated by a classical field, parameterized with quantum and/or empirical data. The conformational energy of the molecule is made up of a sum of bond and nonbond terms. In this approach, only the covalent hydrogen bonded to oxygen or to nitrogen is considered explicitly, whereas the CH_1, CH_2, and CH_3 groups are assumed to be an atomic unit.

The THOR force field is:

$$E = E_b + E_\theta + E_\varphi + E_\omega + E_{vdW} + E_{el}$$

$$E = \frac{1}{2}\sum_n K_{H_n}(r_n - r_o)^2 + \frac{1}{2}\sum_n K_{\theta_n}(\theta_n - \theta_o)^2 + \frac{1}{2}\sum_n K_{\phi_n}(1 + \cos(m\phi_n - \delta_n)) + \frac{1}{2}\sum_n K_{\omega_n}(\omega_n - \omega_o)^2 + \sum_{i<j}\left[\frac{C_{12}(i,j)}{r_{ij}^{12}} - \frac{C_6(i,j)}{r_{ij}^6}\right] + \frac{1}{4\pi\epsilon_o}\sum_{i<j}\frac{q_i q_j}{r_{ij}^2} \quad (13)$$

where E_b is the bond energy term or covalent interaction, described by a harmonic potential between two atoms; E_θ is the angular energy term or harmonic interaction in the bonding angles between three atoms; E_φ is the proper dihedral energy term or term of senoidal dihedral torsion between four atoms; E_ω is the improper dihedral energy term involving four atoms; E_{vdW} is the short distance repulsion and van der Waals attraction, described by the Lennard–Jones potential between pairs of atoms; and E_{el} is the electrostatic interactions (Coulombic potential between pairs of atoms). The first four terms represent interactions between chemically bound atoms and the last two represent interactions between nonbound atoms. The first and second bonded neighbors are excluded from the calculations of nonbonded interactions. The THOR force field is based on the GROMOS package.[16]

The code has been developed for the modeling of molecules of biological interest in aqueous and apolar media, as well as at the interface between them. The software establishes two media with different continuous dielectric constants, ϵ_1 and ϵ_2, separated by an interface. The dielectric discontinuity is taken as an approximation of a cytoplasm/membrane environment. The membrane/water interface is expressed by a discontinuity in the dielectric constant, taking into account the different electrical polarizability of the aqueous and the hydrocarbon phases. Thus, the electrostatic interaction between nonbounded atoms at this interface is renormalized by the influence of the dielectric discontinuity. The polarization field produced at the interface of discontinuity by a point charge can be calculated by the method of images. The method of images is employed to describe the electrostatic interaction between an atom i in a medium with dielectric constant ϵ_1 and an atom j and its image j' in media with dielectric constants ϵ_1 and ϵ_2, respectively. An effective dielectric constant $(\epsilon_1 - \epsilon_2)/2$ is used when i and j are located in different media. A fictitious charge is placed in the opposite phase; the distance and the value of the image charge are fixed by taking the appropriate electrical boundary conditions at the surface. When two charges, i and j, are on the same side of the interface, the potential on i due to j will have a contribution due to the image of j (i.e., j'), so that the Coulomb potential on i will be expressed by:

$$V_i = \frac{1}{4\pi\epsilon_1} q_i \left\{ \frac{1}{r_{ij}} + \frac{\epsilon_1 - \epsilon_2}{\epsilon_1 + \epsilon_2} \frac{1}{r_{ij'}} \right\} \tag{14}$$

where:

$$r_{ij} = \left[(x_i - x_j)^2 + (y_i - y_j)^2 + (z_i - z_j)^2 \right]^{1/2} \tag{15}$$

is the distance between the atoms i and j, and:

$$r_{ij'} = \left[(x_i + x_j - 2x_s)^2 + (y_i - y_j)^2 + (z_i - z_j)^2 \right]^{1/2} \tag{16}$$

is the distance between atoms i and j' and x_s is the Cartesian coordinate of the surface between the two media. When two charges are different sides of the interface, the method of images gives the following result:

$$V_i = \frac{1}{4\pi} \frac{q_i}{(\epsilon_1 + \epsilon_2)^2} \frac{1}{r_{ij}} \tag{17}$$

We note that the aforementioned terms account for the effect of the interface on the pair interaction terms only, with the self-induced field created by a single charge being ignored here. The latter will be a pure solvent effect, which should be corrected by other solvent effects not treated here. Because we are most interested in the molecular conformational charges at the interface, we prefer only to consider the renormalization of the pair interactions, leaving solvent effects for further investigations.

In the following section we present applications for the SMO approach.

Applications

We applied the SMO approach to investigate conformations of some molecular systems. The first application of our approach was to search the range of q_V values that answer the question: *Which q_V or distribution of probability corresponds to a minimum number of steps to find the global minimum energy*?

To answer this question we generated two maps (Figs. 2 and 3) in terms of $q_V \times T \times nC$. nC is the number of cycles needed to obtain convergence in energy. That is, for each (q_V, T), we calculated the number of steps necessary to search the global minimum in cases of H_2O and H_2O_3 molecules.

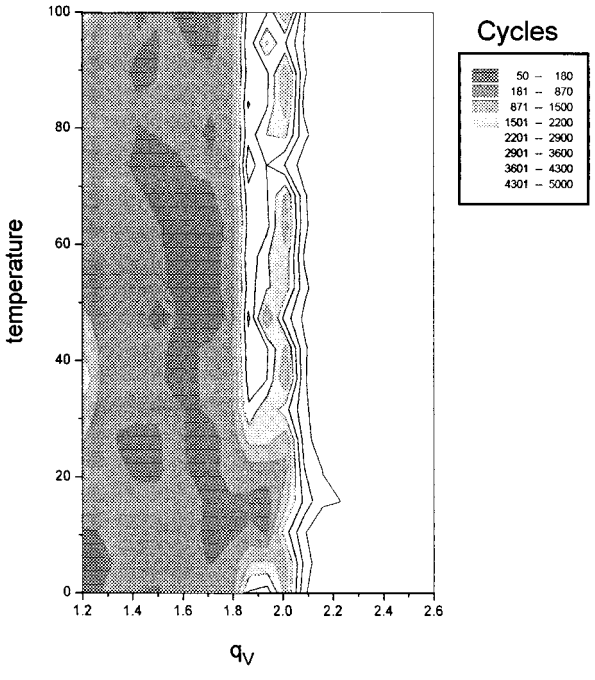

FIGURE 2. Range of the q_V parameter. When q_V is close to 1.7, the algorithm convergence is faster than with other q_V values. This behavior is obtained for the water molecule when we optimize the H—O—H angle.

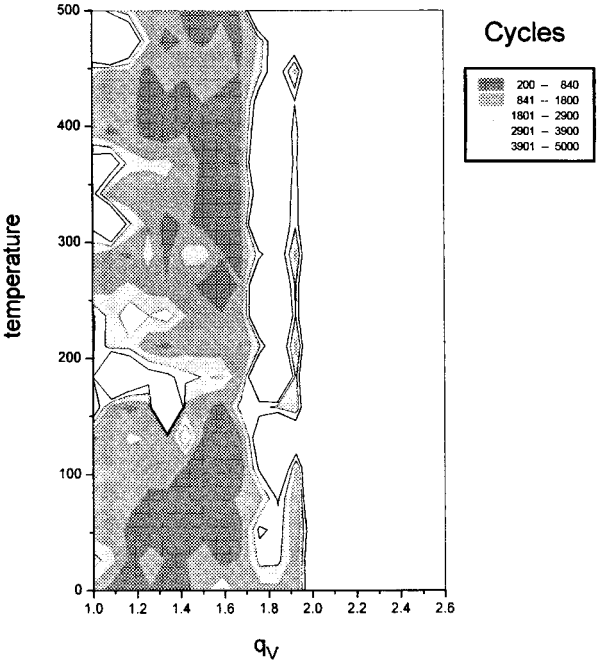

FIGURE 3. Range of the q_V parameter. When q_V is close to 1.6, the algorithm convergence is faster than with other q_V values. This behavior is obtained for the H_2O_3 molecule when we optimize the H—O—O angle.

H_2O (DIMENSION $D = 1$)

Using a fixed H—O distance, we scanned the angle θ ($D = 1$) between H—O—H bonds to investigate the angular energy (rotational barrier) for the H_2O molecules. If we scanned the potential surface in 0.1° steps this results in 3600 cycles necessary to search the angular range (0° to 360°). However, with the random procedure proposed by the GSA algorithm, we obtained the global minimum with less than 180 cycles for $(q_A; q_V) = (1.5; 1.7)$ (Fig. 2). When q_V was close to 1.7 the algorithm convergence was faster than with other q_V values.

H_2O_3 (DIMENSION $D = 2$)

For the H_2O_3 molecule we optimized two ($D = 2$) proper dihedral angles, θ_1 and θ_2 (Figs. 3 and 4), and obtained the global minimum with less than 840 cycles using $(q_A; q_V) = (1.5; 1.6)$ (we note that 3600×3600 cycles is far greater than 840 cycles). For all applications we used the same initial temperature, $T_{q_V} = 300$ K.

Figure 3 shows the range of the q_V parameter. When q_V was close to 1.6 the algorithm convergence was faster than with other q_V values. This behavior was obtained for the H_2O_3 molecule when we optimized the H—O—O angle.

The equilibrium geometry determined, in both cases, agrees qualitatively with the results obtained from a quantum mechanics semiempirical procedure[7]; however, all mappings were obtainable faster using SMO than using the semiempirical method.

Another important result was that the variation range of q_V (Figs. 2 and 3) agreed with the relationship proposed in ref. [17]; that is:

$$\frac{4 + D}{2 + D} \leq q_V \leq \frac{2 + D}{D} \tag{18}$$

Eq. (18) defines the region where q_V is optimized, which corresponds to a minimum number of steps to find the global minimum. D is the space dimension or the number of parameters to be optimized.

POLYPEPTIDES (DIMENSION $D = 36$)

As a second application we used the SMO approach to verify the formation of an α-helix structure with polypeptides. Another goal of this application was to check the potentiality of the SMO method in case of a large molecular system or in case of a large dimension of D. We investigated

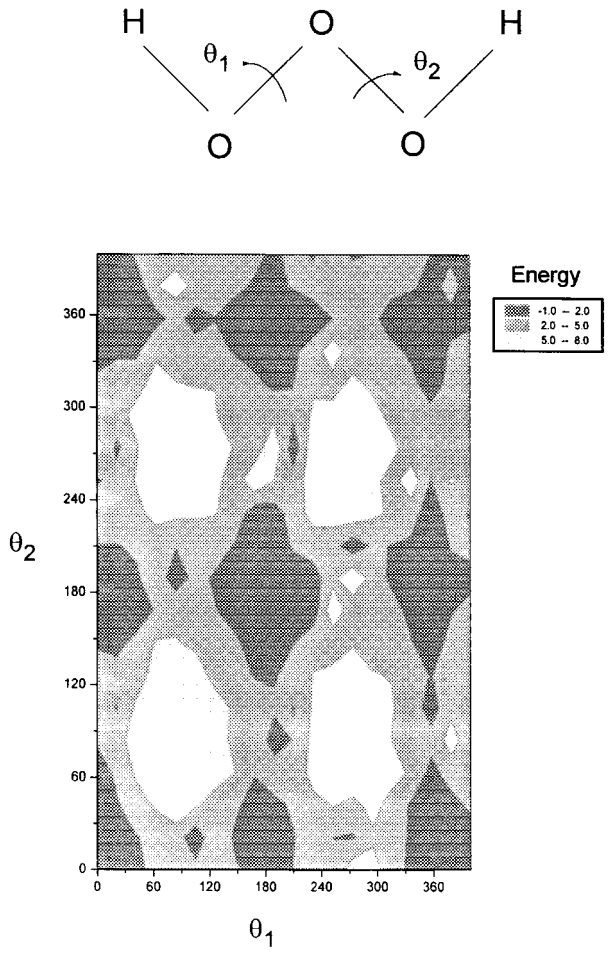

FIGURE 4. The figure shows the potential surface by optimizing the two proper dihedral angles for the H_2O_3 molecule. The angular symmetry is observed in the $\theta_1-\theta_2$ surface.

two structures: pentalanine and icoalanine molecules. These are polypeptides molecules, composed of 5 and 20 alanine residues, respectively.

The search of the global minimum by the SMO approach allows us to map the hypersurface's conformational energy, as shown in Figures 4 and 5 for the H_2O_3 and icoalanine molecules, respectively.

The α-helix (a polypeptide structure) is a rod-like structure. The tightly coiled polypeptide main chain forms the inner part of the rod, and the side chain extends outward in a helical array in low dielectric medium. The α-helix is stabilized by hydrogen bonds between the NH and CO groups of the main chain. The CO group of each amino acid is hydrogen bonded to the NH group of the amino acid situated four residues ahead in the linear sequence. Thus, all of the main chain CO and NH groups are hydrogen bonded. We studied these compounds by optimizing the dihedral angles ω (CH_1—C—N—CH_1), Ψ (N—CH_1—C—N), and Φ (C—N—CH_1—C).

We showed that pentalanine does not form a stable α-helix structure, probably because the number of hydrogen bonds is insufficient to maintain the helical array. We optimized the Ψ, Φ, and ω dihedral angles and obtained, using the SMO approach, a global minimum, which does not correspond to the helical array. Furthermore, the "most frequent" Ψ, Φ, and ω dihedral angles found in the THOR GSA run do not correspond to α-helix structures.

On the contrary, the icoalanine molecule is an α-helix structure. The following improper angles are expected for an α-helix structure: $\omega = 180°$, $\Psi = -40°$, and $\Phi = -60°$. The ω torsion angle has two minima, one at 0° and the other at 180°. The latter value is always observed in biological structures, except for special situations with proline residues. To simplify the calculation we set $\omega = 180°$. Figure 5 shows the Φ, Ψ conformational energy surface obtained and also shows, as expected, that the global minimum occurs at the angles $\Phi = -60°$ and $\Psi = -40°$.

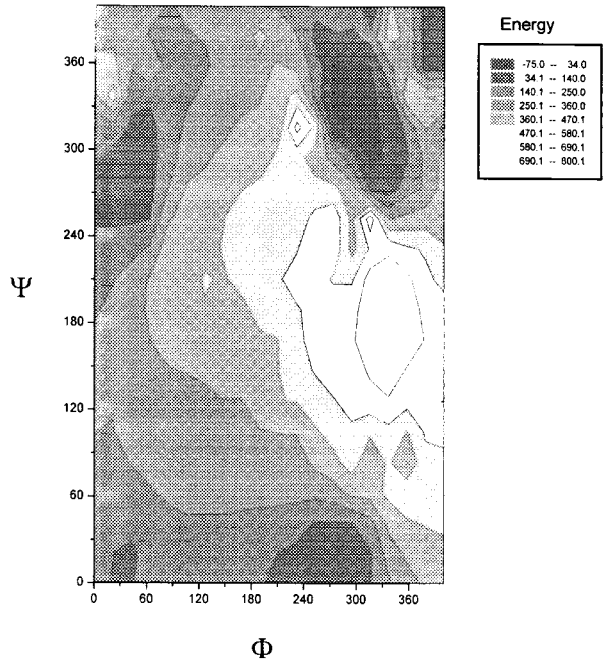

FIGURE 5. The global minimum for the Φ and Ψ angles is close to 300° (−60°) and 320° (−40°), respectively. This behavior, for the icoalanine molecule, is an α-helix structure.

We can obtain the α-helix structure, simulating all Φ, Ψ pairs, in a few minutes, using an IBM Risc-6000 workstation. With $q_A = 1.5$, $q_V = 2.0$, and $T_{q_V} = 100$, the simulation takes 3673 to 100,000 cycles for 18 Φ, Ψ pairs ($D = 36$). Alternatively, using MD, we would have waited several days for simulation! Furthermore, depending on the initial condition, we do not obtain an α-helix structure, because MD only guarantees a dynamical structure, which is frequently a local minimum, due to the fact that protein folding is not in the MD time scale.

We note that, in order to compare the SMO method with the usual Monte Carlo method, a similar simulation was done in ref. 16. In this last case, the folding of the α-helix is reached in 100 *million* cycles, which makes the SMO a promising method for protein folding studies.

All force field parameters used in the applications presented in this article, are listed in the Tables Ia–e. The atomic nomenclature used is H (hydrogen), HO (hydroxyl hydrogen), CH_1 (aliphatic GH group), CH_3 (aliphatic CH_3 group), N (nitrogen), NT (terminal nitrogen), O (oxygen), and OA (hydroxyl oxygen).

Concluding Remarks

We conclude from this preliminary study that the SMO approach is an excellent qualitative and quantitative indicator of conformational molecular

TABLE Ia.
Bond Stretching Parameters.[a]

Atomic bond	K_{H_n}	r_o
O—H	750.00	1.00
O—O	750.00	1.20
OA—HO	750.00	1.00
NT—H	895.00	1.00
NT—CH_1	900.00	1.47
N—CH_1	900.00	1.47
N—H	895.00	1.00
C—N	1000.00	1.33
C—O	1200.00	1.23
C—OA	900.00	1.36
CH_1—CH_3	800.00	1.53
CH_1—C	800.00	1.53

[a] K_{H_n} expressed in kcal mol^{-1} Å^{-2}, and r_o in Å.

TABLE Ib.
Bond-Angle Bending Parameters.[a]

I—J—K angle	K_{θ_n}	θ_o
H—O—H	95.00	109.50
H—O—O	70.00	120.00
H—N—CH_1	90.00	115.00
H—NT—H	80.00	120.00
H—NT—CH_1	90.00	120.00
CH_1—C—N	120.00	115.00
CH_1—C—O	120.00	121.00
CH_1—C—OA	120.00	115.00
CH_3—CH_1—C	110.00	109.50
C—N—H	70.00	123.00
C—N—CH_1	120.00	122.00
C—OA—HO	95.00	109.50
NT—CH_1—C	110.00	109.50
NT—CH_1—CH_3	110.00	109.50
N—CH_1—C	110.00	109.50
N—CH_1—CH_3	110.00	109.50
O—O—O	120.00	124.00
O—C—N	120.00	124.00
O—C—OA	120.00	124.00

[a] K_{θ_n} expressed in kcal mol^{-1} rad^{-2}, and θ_o in degrees.

TABLE Ic.
Improper Dihedral Angle Parameters.[a]

Improper angle	K_{ϕ_n}	ϕ_o
CH_1—X—Y—CH_3	80.00	35.26
C—X—Y—O	40.00	0.00
N—X—Y—H	40.00	0.00
NT—X—Y—CH_1	40.00	0.00

[a] K_{ω_n} expressed in kcal mol^{-1} rad^{-2}, and ω_o in degrees.

TABLE Id.
Improper Dihedral Angle Parameters.[a]

Proper angle	K_{ω_n}	ω_o
X—NT—CH_1—Y	0.90	0.00
X—CH_1—C—Y	0.10	0.00
X—C—N—Y	8.00	180.00
X—N—CH_1—Y	0.10	180.00
X—C—OA—Y	4.00	180.00

[a] K_{ϕ_n} expressed in kcal mol^{-1}, and ϕ_o in degrees.

TABLE Ie.
Atomic Mass Measurements.[a]

Atom	Mass
H	1.008
HO	1.008
CH_1	13.019
CH_3	15.035
N	14.006
NT	14.006
O	15.999
OA	15.999

[a]Data expressed in atomic units.

preferences.

- The GSA method, compared with the gradient descent approach, or other conventional approaches, shows the advantage of directly obtaining the global minimum, while scanning the potential hypersurface during this searching.
- Furthermore, unlike the usual molecular dynamics (MD) method, the SMO is force independent; that is, we obtain the optimized conformation without calculating the force, and only potential energy is involved. Therefore, we do not need to know the conformational energy gradient to arrive at equilibrium conformations.
- We emphasize that, using the MD method, within reasonable computer time, it is not guaranteed that a global minimum structure will be crossed or reached during the simulation. However, the SMO method guarantees that a global minimum will be attained, at least as shown in this article for peptides of about 20 residues. In addition, this procedure enables us to map out minima while searching for the global minimum.
- The GSA method converges quickly when the q_V parameter falls within eq. (18).
- We obtained the same behavior as in ref. 17 by using an inverse visiting distribution probability, calculated by eq. (11).

We hope to apply the SMO method to simulate a peptide at the membrane interfaces and to investigate other molecular structures, such as pharmaceuticals, proteins, and DNA, which are more complex in structure than those used in this study.

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